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Comparison of the Effect of Ethanol Extracts of *Phaleria macrocarpa (scheff.Boerl)* Fruit and Metformin on the Kidney Function of Hyperglycaemic Rat Models

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Abstract

Diabetes mellitus is a disease that often causes diabetic nephropathy complications due to persistent hyperglycaemia. *Phaleria macrocarpa (scheff. Boerl)* is one of the plants that has been widely used in the treatment of diabetes mellitus, but its effect on the risk of diabetic nephropathy is still unknown. A dose of 300mg / 200gbb / day is known as an effective dose that can significantly reduce blood sugar levels in diabetic rat. This study aims to compare the effect of *Phaleria macrocarpa (scheff. Boerl)* fruit extracts on urea and creatinine levels as a parameter of kidney function in hyperglycaemic mouse models. The study was carried out experimentally using the post-test only with control group design. All rats were induced with 40 mg / 200gbb of Streptozotocin (STZ) to experience hyperglycaemia. Group I as negative control was given aquades. Group II was given ethanol extract of *Phaleria macrocarpa (scheff. Boerl)* with a dose of 300 mg / 200gbw / day. Group III was given Metformin at a dose of 150 mg / 200gbw / day. The research data were statistically analyzed with α <0.05; CI95%. The mean of urea levels in Group I (79.80 ± 25.09 mg / dl), II (76.00 ± 22.59 mg / dl and III (59.60 ± 6.35 mg / dl). Kruskal-Wallis test results showed no significant difference in urea levels between treatment groups (p value = 0.273; CI95%). The mean of creatinine levels in Group I (0.68 ± 0.07 mg / dl), II (0.63 ± 0.14 md / dL) and III (0.98 ± 0.25 mg / dL). One Way Anova and Post hoc test results showed a significant difference in mean creatinine levels between Groups I and III (p = 0.014; 95% CI) and II with III (p value = 0.006; CI95%). the results of this study can be concluded that the extract of *Phaleria macrocarpa (scheff. Boerl)* fruit flesh at a dose of 300 mg / 200gbb has better effectiveness than metformin dose 150 mg / 200gbb in repairing the kidney function of hyperglycaemia rats.

Keywords = *Phaleria macrocarpa (scheff. Boerl)* extract, Kidney function, Hyperglycemia, Metformin, Streptozotocin

Abstrak

Diabetes melitus merupakan penyakit yang sering menimbulkan komplikasi nefropati diabetika akibat hiperglikemia yang menetap. *Phaleria macrocarpa (scheff. Boerl.)* merupakan salah satu tanaman yang telah banyak digunakan dalam pengobatan diabetes melitus tetapi efek terhadap risiko nefropati diabetika masih belum banyak diketahui. Dosis 300mg/200gbb/hari diketahui sebagai dosis efektif yang mampu menurunkan kadar gula darah secara bermakna pada tikus model diabetes. Penelitian ini bertujuan untuk membandingkan pengaruh pemberian ekstrak daging buah *Phaleria macrocarpa (scheff. Boerl.*) terhadap kadar ureum dan kreatinin sebagai parameter fungsi ginjal pada tikus model hiperglikemia. Penelitian dilakukan secara eksperimental desain *post test only with control group*. Semua tikus diinduksi dengan 40 mg/200gbb Streptozotocin (STZ) hingga mengalami hiperglikemia. Kelompok I sebagai kontrol negatif diberi aquades. Kelompok II diberi ekstrak ethanol *Phaleria macrocarpa (scheff. Boerl.)* dengan dosis masing-masing 300 mg/200gbb/hari. Kelompok III diberi Metformin dengan dosis 150 mg/200gbb/hari. Data penelitian dianalisis secara statistik dengan α<0,05;IK95%. Rerata kadar ureum pada Kelompok I (79,80±25,09 mg/dl), II (76,00±22,59mg/dl dan III (59,60±6,35 mg/dl), Hasil uji Kruskal-Wallis menunjukan tidak perbedaan yang bermakna kadar ureum antar kelompok perlakuan (nilai p=0,273;IK95%). Rerata kadar kreatinin Kelompok I (0,68±0,07 mg/dl), II (0,63±0,14 md/dL) dan III (0,98±0,25 mg/dL), Hasil uji One Way Anova dan Pos hoc terdapat perbedaan bermakna rerata kadar kreatinin antara Kelompok I dan III (p=0,014;IK 95%) dan II dengan III (nilai p=0,006;IK95%), Hasil penelitian ini dapat disimpulkan bahwa ekstrak daging buah *Phaleria macrocarpa (scheff. Boerl.*) dosis 300 mg/200gbb memiliki efektivitas yang lebih baik dibandingkan metformin dosis 150 mg/200gbb dalam memperbaiki fungsi ginjal tikus model hiperglikemia.

Kata kunci = Ekstrak *Phaleria macrocarpa*, Fungsi Ginjal, Hiperglikemia, Metformin, Streptozotocin.

INTRODUCTION

Diabetes Mellitus able to increase about a two-fold risk for a wide range of vascular diseases, independently from other conventional risk factors.[1] In 2012, there were about 1.5 million deaths caused by diabetes regarding to increasing of cardiovascular risk and other disease. The amount of death attributable to hyperglycaemia that occurred under age 70 years old more in development countries than in a big country.[2]

One serious disease that is a complication of diabetes is diabetic nephropathy, due to microvascular disorders that accompany chronic hyperglycaemia in diabetes.[3] Diabetic nephropathy is also the biggest cause of morbidity and mortality in diabetic patients.[4] Diabetic nephropathy develops in about 30-40% of diabetic patients.[5] The prevalence of diabetic nephropathy was reported in 29.4% of diabetics in Thailand, 20.8% in the Philippines and about 2, 0-39.3% in Indonesia.[2]

Hyperglycaemia is an important risk factor for the development of diabetic nephropathy. Persistent hyperglycaemia can increase ROS production and interact with deoxyribonucleic acid (DNA) and proteins causing oxidative stress and cell damage.[6,7] In addition, the pathogenesis of diabetic nephropathy is also associated with activation of intracellular signalling molecules such as protein kinase-C (PKC), and accumulation of advanced glycation end products (AGE).[8]

Hyperglycaemia can also activate the release of nuclear factor-κB as one of the main mediators in the regulation of various types of pro-inflammatory and pro-atherosclerotic target genes in vascular smooth muscle as well as activating macrophages.[9,10] Increased PKC-β2 activity can also trigger endothelial of blood vessels to produce prostaglandin E2 and thromboxane A2, substances that alter the permeability and vascular response to Angiotensin II. In addition, Protein kinase-C also contributes to the accumulation of microvascular matrix proteins by inducing transforming growth factor (TGF) -β, fibronectin, and type IV collagen in mesangial cells.[11] Eventually this condition will lead to vascular disorders to various organs, including the kidneys and cause to renal impairment which characterized with declining of renal function and rising of serum urea and creatinine levels.[10,12] Therefore, Good hyperglycaemic control can reduce the risk of renal disease in diabetes patient. The intensive glucose control can slow Glomerular Filtration Rate (GFR) loss and possibly progression to diabetic nephropathy.[13]

Phaleria macrocarpa (scheff. Boerl.) fruit has long been used in traditional medicine as an anticancer drug, allergies, diabetes mellitus drugs, heart disease, liver, skin, hypertension, stroke, aches, and flu.[14] Results of several previous studies indicate that Extracts *Phaleria macrocarpa (scheff. Boerl.)* fruit has a hypoglycaemic effect through inhibition of the activity of the α-glucosidase enzyme and repairing pancreatic beta cell damage.[15,16] In addition, *Phaleria macrocarpa (scheff. Boerl.)* fruit extract can also repair damaged blood vessels of diabetic mice by increasing the regeneration ability of blood vessel wall cells.[17] inhibiting the expression of growth factors (VEGF and TGF-β) in diabetic mouse kidney tissue so it is thought to have a potential nephroprotective effect.[18]

Phaleria macrocarpa (scheff. Boerl.) fruit contains many active compounds which have various pharmacological effects. The active compounds consist of flavonoids, phenolics, alkaloids, tannins, saponins, and terpenoids. Phenolic and flavonoid compounds are the highest component of compounds found in the extract of *Phaleria macrocarpa (scheff. Boerl.)* fruit.[14] Some flavonoid compounds that play an important role in the treatment of diabetes such as Mangiferin,[19] Quercetin,[20,21]and Naringin.[20]

Both Mangiferin, Quercetin and Naringin have hypoglycaemic effects. Mangiferin and Quercetin work through a mechanism of inhibiting the activity of the enzyme α-glucosidase thereby reducing glucose absorption in the intestine.[19] In addition, Mangiferin also increases peripheral glucose use by increasing activity of glucose-6-phosphate dehydrogenase enzyme and inhibiting gluconeogenesis, while Quercetin can also decreases haemoglobin A1c (HbA1c) levels in diabetic rat models without affecting insulin activity.[21,22]

Metformin is a biguanide oral anti-diabetes drug which has mechanism of action through increasing insulin receptor sensitivity. The American Diabetes Association (ADA) has established metformin as a first-line drug in the pharmacological management of type 2 DM and is the most widely used drug in the world.[23] Metformin also has the effect of reducing glucose production in the liver and kidneys (gluconeogenesis) and inhibits glucose absorption in the intestine. In addition, Metformin also increases the sensitivity of muscle tissue and adipose to insulin thereby increasing the use of peripheral blood sugar and decreasing the glucagon levels in plasma.[24] In other studies, metformin can repair rat kidney cells induced by gentamicin which is thought to be related to inhibitory effects on the formation of reactive oxygen species (ROS) in kidney tissue, decreases lipid peroxidation products (thiobarbituric acid reactive substances) in kidney endothelial cells and increase total plasma antioxidant systems.[25]

The aims of this study was to compare the pharmacological effects of *Phaleria macrocarpa (scheff. Boerl.)* fruit extracts and metformin on the kidney function of diabetic rat models which are reviewed based on plasma urea and creatinine levels. Is *Phaleria macrocarpa (scheff. Boerl.)* fruit extract can repair kidney function of diabetic rats that have the potential to experience complications of diabetic nephropathy and whether the effect is better than

metformin which has been used as one of the standard medicines for diabetes? In a preliminary study, it was found that a dose of 300 mg / 200 gbw / day of *Phaleria macrocarpa (scheff. Boerl.)* fruit extract could significantly decrease the blood sugar levels of diabetic rat models. Therefore, the dose was used in this study.

METHOD

This is an experimentally research which conducted with post-test only with control group design. The research procedures have been approved by the Medical and Health Research Committee (MHREC) Faculty of Medicine, Gadjah Mada University. fifteen of healthy rats, 2-3 month age and body weigh between about 150 - 200g were housed in wire cages at 25-27 °C and were adapted for a week at Pharmacology laboratory. The rats were divided by randomize into 3 groups. All rats were induced with 40 mg/200gbw of Streptozotocin (STZ) to experience hyperglycaemia. Group I as a negative control were given drinking water. Group II were given the ethanol extract of *Phaleria macrocarpa (scheff. Boerl.)* fruit flesh with doses of 300 mg/200gbw/day orally and Group III was given Metformin at a dose of 150 mg/200gbw/day orally. On the 22nd day of treatment, blood specimens were taken for examination of urea and creatinine levels. The blood sugar was examined before and after treatment for confirmation of hyperglycaemia condition.

Materials and Instruments

This research uses ingredients such as 96% ethanol solvent, 1% Carboxymethyl Cellulose (CMC), Metformin HCL 500mg (*Forbetes* 500®), Streptozotocin (STZ), kit urea FS reagents (*Diasys*®), kit creatinine FS reagents (*Diasys*®) and GOD-PAP reagents. Meanwhile, instruments used include centrifuges (Kubota®), water tubes, spectrophotometers (Optima® Sp 300), micro pipettes (10 µl and 1000 µl), digital scales 0.00000-100,000g (Dragon® 303) by Mettler Toledo Groups, Vortex-mixer, Oral sonde 1.5 x 80 mm and evaporator.

Extract Preparation

Phaleria macrocarpa (scheff. Boerl.) fruit flesh was extracted using maceration techniques within 96% ethanol. The flesh of *Phaleria macrocarpa (scheff. Boerl.)* fruit was washed, small sliced and dried in the sun but covered with a black cloth to keep the active ingredients. The dry *Phaleria macrocarpa (scheff. Boerl.)* fruit flesh were mashed into powder. Fifty grams of powder was extracted in 500 mL 96% ethanol by maceration (72h) Then, using a rotary vacuum evaporator to vaporize the remaining ethanol 96% solvent and then the extract is dried in a water-bath at a temperature of 60-70 ^{o}C until it thickens into a paste.[26]

Phaleria macrocarpa (scheff. Boerl.) fruit were obtained from Merapi Herbal Farma, Yogyakarta, Indonesia and identified at Taxonomy Laboratory, Faculty of Biology, Jenderal Soedirman University.

Examination of Blood Sugar, Urea and Creatinine Levels

Blood sample was collected from each research animal by retro-orbital puncture after an 8-12 hours overnight fast. The collected blood specimens were centrifuged to obtain serum samples. The separated serum samples were analysed for sugar, urea and creatinine. The blood sugar levels check is carried out using the GOD-PAP method by using a spectrophotometer at a wavelength of 546 nm. Urea levels was determined by kit urea FS reagents, while Creatinine levels was by kit creatinine FS reagents by using a spectrophotometer at a wavelength of 546 nm. All these methods were based on manufacturer's instructions.[27,28]

Statistical Analysis

The differences of serum urea levels among groups of the study were tested with Kruskal-Wallis test while the differences of serum creatinine levels among groups of the study were tested with One-Way Anova test followed by post hoc test (LSD).

RESULT

The fasting blood sugar levels were measured to find out whether a hyperglycaemic rat models has been formed in all study groups or not before given the extract of *Phaleria macrocarpa (scheff. Boerl.)* fruit and Metformin. The fasting blood sugar levels were measured using the GOD-PAP method with a spectrophotometer at a wavelength of 546 nm. The measurement results showed that all rats in all of study groups had normal fasting blood sugar levels before being induced with Streptozotocin (107.40-116.00mg / dl) and after being induced, all mice experienced an increase in blood sugar levels that exceeded normal fasting blood sugar levels (healthy), which is more than 122.3 + 16.28 mg / dl.[29] The mean blood sugar levels in each study group can be seen in table 1. Therefore, in this study a hyperglycaemia mouse model can be well formed.

Tabel 1. The mean blood sugar levels in each study group

Groups	n	Initial (mg/dL)	Post-Induction (mg/dL)
I	5	116,00±2,83	302.80±110.88
II	5	113,40±6,23	344,20±72,11
III	5	114,20±5,76	357,80±41,57

n=sample size

The results of urea levels examination in each study group showed that the negative control group (hyperglycaemia models without treatment) experienced the highest increase in urea levels (79.80 ± 25.09 mg / dL) compared to the other study groups that were given treatment, both with the extracts of *Phaleria macrocarpa (scheff. Boerl.)* fruit and Metformin. The study group that was given the treatment of Metformin, had the lowest urea levels

(59.60 ± 6.35 mg / dL) while the average urea levels in the *Phaleria macrocarpa (scheff. Boerl.)* fruit extract group was 76.00 ± 22.59 mg / dL, as seen in figure 1. When compared with the normal urea level of healthy rat (17,1 or between 12.3-24,6 mg / dL), all mice in all study groups had a urea level of 3.5-4.7 times higher.[30] The results of statistical analysis using the Kruskal-Wallis Test showed that there was not significantly difference on the serum urea levels among the study groups (p-value = 0, 273; CI95%)

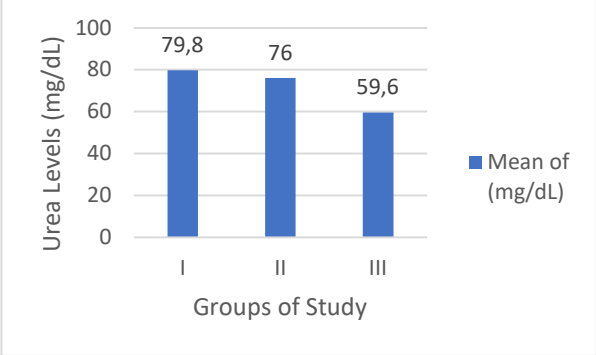

Figure 1. The serum urea levels of each study group

The results of serum creatinine levels examination it was found that the lowest creatinine levels were found in group 2 treated with the extracts of *Phaleria macrocarpa (scheff. Boerl.)* fruit (0.63 ± 0.14 mg / dL) and the highest was found in group 3 treated with Metformin (0.98 ± 0.25 mg / dL). Group 1 as a negative control had a mean creatinine level of 0.68 ± 0.07 mg / dL, as showed in figure 2. When compared with the normal standard mean of Creatinine levels in healthy mice (0.3 or between 0.2-0.5 mg / dL), serum creatinine levels increase 2-3 times in all of the Study Groups and even in group 3 can reach more of 3 times of healthy rat.[30]

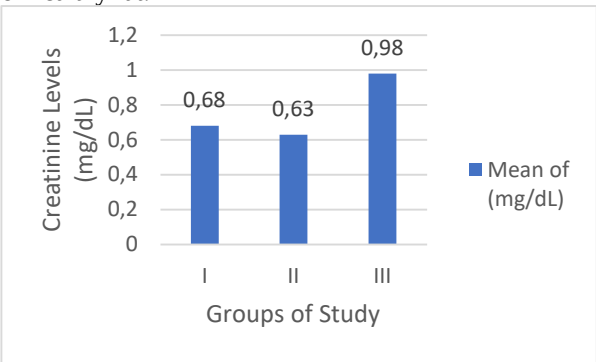

Figure 2. The serum creatinine levels of each study group

Statistical analysis using the One-way Anova test showed that there were significant differences in mean of serum creatinine levels between study groups (p-value = 0.012; CI95%). In the post hoc test with LSD, it was found that there was a significant difference the average of serum creatinine levels between group I (negative control) and group III who were given Metformin treatment (p-value = 0.014; CI95%) and between group II who were treated with the extracts of Phaleria macrocarpa fruit with group III (p-value = 0.006; CI95%)

DISCUSION

The hyperglycaemia that occurred in this study was caused by Streptozotocin which after being given would selectively accumulate in the β cells of the islets of Langerhans through the glucose transporter (GLUT 2) and cause a series of damage processes in β cells. Streptozotocin causes changes in DNA, activates reactive oxygen species (ROS), forms superoxide anions in mitochondria and increases xanthine oxidase activity which inhibits the Krebs cycle and decreases ATP production. This series of processes resulted in the death of β cells in the islets of Langerhans, thereby inhibiting pro-insulin synthesis and ultimately inducing hyperglycaemia in all experimental animals.[31]

Persistent High blood sugar levels (hyperglycaemia) will activate oxidative stress reaction pathways in cells, including those in the kidney organs. In general, kidney cells are very susceptible to extracellular hyperglycaemia because the kidneys have transporters that do not require insulin. Exposure to chronic hyperglycaemia in renal glomerular mesangial cells has been shown to increase GLUT 1 and increase influx of glucose into cells.[32] Changes in the expression of transporters in glomerular cells and kidney tubules has a strong contribution to renal cells damage regarding increasing of intracellular glucose levels that activate oxidative stress pathways on the pathophysiology of kidney dysfunction in diabetes (diabetic nephropathy).[32,33]

In this study, impaired kidney function was demonstrated by elevated serum urea and creatinine levels exceeding normal levels in healthy rat. Increasing of urea and creatinine levels on impaired renal function due to hyperglycaemia were seen in group I (negative control). In this group, the mean of serum urea levels could reach 3.5-4.7 times of the healthy rat urea levels while the serum creatinine levels could reach 2-3 times. The results of this study, can support the theory and results of previous studies which state that hyperglycaemia can cause kidney damage or known as diabetic nephropathy.

In this study, the potency of nephroprotective effect of the extracts of *Phaleria macrocarpa (scheff. Boerl.)* fruit on hyperglycaemia rat models has been evaluated and showed that this extract was able to decrease urea and creatinine levels in experimental animals. In this study, the potential nephroprotective effect of *Phaleria macrocarpa (scheff. Boerl.)* fruit extracts in hyperglycaemic rat models was evaluated and showed that this extract was able to decrease serum urea and creatinine levels in experimental animals. The results of this study indicated that the active compound contained in *Phaleria macrocarpa (scheff. Boerl.)* fruit extract has a pharmacological effect that is able to

repair kidney cell damage due to hyperglycaemia caused by damage to β-cells of the islet of the pancreatic Langerhans.

As it is known that *Phaleria macrocarpa (scheff. Boerl.)* fruit extract contains several important active compounds that have pharmacological effects such as hypoglycaemia, anti-oxidant and anti-inflammatory effects.[15,19] Flavonoid compounds (Mangiferin, Quercetin and Naringin) have an important role for the hypoglycaemia effect of *Phaleria macrocarpa (scheff. Boerl.)* fruit extracts through several mechanisms, such as inhibition of the activity of α-glucosidase enzymes in the intestine, inhibits gluconeogenesis, increases sensitivity of insulin receptors in peripheral tissues and other mechanisms that all of these mechanisms cause a decrease in blood sugar levels. [19,21]

Decreased blood sugar levels in experimental animals will stop the process of kidney damage that occurs due to the induction of hyperglycaemia by reducing oxidative stress reactions in glomerular cells, tubules and other kidney cells, stopping damage to cell DNA, repairing the mitochondrial system in producing ATP and ultimately stimulating regeneration and repair of kidney cells.

Besides the effects of hypoglycaemia, another important effect possessed by active compounds in the extract of *Phaleria macrocarpa (scheff. Boerl.)* fruit is the antioxidant effect. Anti-oxidant effect is very important in the process of controlling complications of diabetic nephropathy. This is considering that one of pathogenesis pathway of diabetic nephropathy through the oxidative stress pathway due to the activation of the reactive oxygen species (ROS) system by hyperglycaemic conditions. The oxidative stress pathway is an important pathway that induces damage and cell death resulting in impaired organ function. Therefore, the oxidative stress process is one of the targets of active compounds which have anti-oxidant effects.

In this extract, the anti-oxidant effect is mainly played by alkaloids, saponins and flavonoids compounds. Among these three compounds, flavonoids have the highest anti-oxidant effect.[20]These active compounds work by increasing the activity of antioxidant enzymes and decreasing free radicals so as to prevent further oxidative stress.[34]

Another effect of the active compound in *Phaleria macrocarpa (scheff. Boerl.)* fruit extract is the anti-apoptotic effect played by benzophenone glycoside derivatives (similar to the *phalerin* compound contained in the leaves of *Phaleria macrocarpa (scheff. Boerl.)*. Anti-apoptotic effect occurs through suppression of the activity of Caspase-3 thereby suppressing kidney cell death and increasing proliferation to repair cell damage that occurs.[35]All of these effects, both the effects of hypoglycaemia, antioxidants and anti-apoptosis, form a protective effect and repair of kidney cells from damage caused by hyperglycaemia.

Effect of Metformin on serum urea levels showed a better effect than the extract group and the control group. The Metformin group (group III) had the lowest serum urea levels among the three study groups. However, on examination of serum creatinine levels, the group treated with Metformin actually showed a significant increase in serum creatinine levels compared to the extract and negative / sick control groups. In the examination of serum creatinine levels, the group treated with extract of *Phaleria macrocarpa (scheff. Boerl.)* fruit had the lowest serum creatinine levels. Why does this happen?

In general, Metformin is an antihyperglycemic drug that works without affecting insulin secretion. This drug does not cause insulin secretion stimulation on B cells of Langerhans Islets to reduce blood sugar levels but works through several other mechanisms, such as reducing hepatic and renal gluconeogenesis, inhibiting glucose absorption in the intestine, increasing the use of blood sugar by peripheral tissues and decreasing glucose levels in plasma.[24]

Other mechanisms of Metformin to prevent complications of diabetes are through improved glycogenesis processes, increased sensitivity of insulin receptor, increased carbonyl compounds, and the formation of AGEs so as to prevent glucotoxicity and reduce oxidative stress due to free radical formation.[36]

Metformin also has an antiapoptotic effect by suppressing caspase-3 activity, stimulating the synthesis of Glucagon Like Peptide-1 (GLP-1) and secretion of endocrine L cells in the intestine that play a role in regulating cell proliferation. Through this mechanism, Metformin has the effect of preventing excessive cell death and is able to stimulate cell regeneration for the repairing of organ function. [24,36]

But why in this study, Metformin did not show good effectiveness in inhibiting and repairing impaired kidney function in hyperglycaemic rats? An analysis of this problem might be explained by the pharmacokinetic properties of this drug. Metformin is given orally and will experience absorption in the intestine. Metformin does not bind to plasma proteins, is not metabolized in the body and is excreted through the kidneys. When kidney damage occurs, Metformin cannot be excreted properly and accumulates in the blood. Therefore, it can potentially experience intoxication in the form of over- pharmacodynamic effects. One of the dangerous effects is the inhibition of gluconeogenesis which can interfere with lactic acid metabolism in the liver so that it can cause lactic acidosis in hyperglycaemic mouse models. This condition can ultimately increase damage to cells and organs including the kidneys.[24]

In this study, the possibility of metformin intoxication was demonstrated by an increase in creatinine levels more than 3-fold compared to normal

levels of creatinine levels in healthy rat. In the statistical analysis, elevated creatinine levels in the group treated with Metformin showed significant differences compared to the extract and control groups. Therefore, administration of Metformin in hyperglycaemic conditions that have shown kidney damage needs to be considered to be discontinued although further research is still needed in order to find other scientific facts that support this truth.

The results of this study have shown a potency of nephroprotective effect on *Phaleria macrocarpa (scheff. Boerl.)* fruit extracts. However, the nephroprotective effect that occurred in this study has not shown good efficacy. Decreased levels of urea and creatinine that occur have not been able to reach the levels equivalent to normal levels of urea and creatinine in healthy rat. This does not mean that this extract cannot be used for medicinal purposes. Research on the extract of *Phaleria macrocarpa (scheff. Boerl.)* fruit still needs to be continued with a different approach and modification. One factor that has not been revealed is related to the characteristics of "time-dependent effect" which allows the extract to work optimally (causing high efficacy) when given in sufficient time to cause the expected therapeutic effect. Therefore, what is likely to occur in this study is the time of administration of the extract which has not been able to show a true nephroprotective effect so that it has not been able to reduce urea and creatinine levels to the maximum. For this reason, further research is needed with administration of extracts longer and more variation in dosage.

CONCLUSION

The results of this study can be concluded that the extract of *Phaleria macrocarpa (scheff. Boerl)* fruit flesh at a dose of 300 mg / 200gbb more effective than metformin dose 150 mg / 200gbb in repairing the kidney function of hyperglycaemia rats. however, it is need the further research with a different approach and modification, especially related with duration of the extract administration.

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